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(54) Derivatives of 4-(2,4-difluoro-biphenylyl)-2-methyl-4-oxo-butanoic acid.

(57) This invention relates to substances represented by Formula (I), wherein X stands for either OR in which R is an alkyl of 1 to 4 carbon atoms, or NHR in which R is an alkyl of 1 to 4 carbon atoms, or a $(CH_2)_nNR'_2$ group wherein n is 2 or 3 while R' is a methyl or ethyl group; eventually X may represent morpholinyl. Also considered are salts of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid with appropriate inorganic or organic bases represented by Formula (II) wherein B^+ is either an alkaline metal cation, alkaline earth cation, cyclohexylamine cation, or lysine cation. Said substances are characterized by anti-inflammatory properties comparable to (and greater than) the initial acid while simultaneously said modifications of their physico-chemical properties broaden the possibilities of their therapeutic application.

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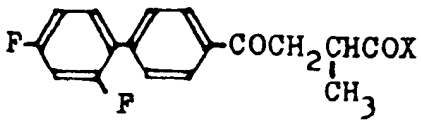
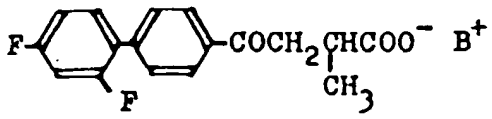
This invention relates to 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid having the following general formula (I)



(I)

wherein X stands for OR in which R is an alkyl of 1 to 4 carbon atoms, or NHR in which R is an alkyl of 1 to 4 carbon atoms, or a $(CH_2)_nNR'_2$ group wherein n is 2 or 3 while R' is a methyl or an ethyl group; eventually X may represent morpholinyl. This invention further relates to salts of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid with appropriate inorganic or organic bases represented by the general formula (II)



(II)

wherein B^+ is either an alkaline metal cation, alkaline earth cation, cyclohexylamine cation, or lysine cation.

Recently a significant prolonged anti-inflammatory effect of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid has been recognized (CS-AO 243 570). An analogous anti-inflammatory effect was found in several functional derivatives and salts of said acid. Some of the substances of general formulae (I) and (II) are characterized by physico-chemical properties, incl. increased solubility in water, which broaden their therapeutic application without any noticeable decrease of their anti-inflammatory effect. Changes in lipophility eventually differing biotransformation of esters and amides in comparison with the free acid may influence the pharmacokinetic behaviour of these derivatives. Results of the pharmacological evaluation of substances (I) and (II) are summarized in Table (I). Simultaneously, these substances are characterized by low toxicity, incl. a low ulcerogenic effect. They may be used for the preparation of therapeutic compositions which may contain the effective substance in combination with pharmacologically acceptable ingredients, liquid or solid, which are usually used in the manufacture of application forms.

Example 1

Ethoxycarbonylmethylamide 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid

5.0 g of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid is dissolved in a mixture of 35 ml dimethylformamide and 150 ml dichlormethane. 2.1 g N-ethylpiperidine is added to the solution and 2.05 g ethylchloroformiate is added after cooling to -15 °C. After stirring for 30 minutes at -15 °C the mixture is cooled to -30 °C and 1.7 g glycineethylester in 35 ml dichlormethane is added. The mixture is left at room temperature to warm up to 20 °C and at this temperature it is stirred for 2 hours. Thereafter, the mixture is consecutively washed 3 times in a separation funnel in 100 ml 5% $NaHCO_3$, once in 100 ml H_2O, 3 times in 100 ml 1 N HCl, and once again in 100 ml H_2O.

Water is adsorbed by Na_2SO_4 from the organic part which is then dried by evaporation and the crystalline residue is purified by crystallization in acetone. Yield: 4.3 g (67.2 % theor.) of the ethoxycarbonylmethylamide (melting point 95-96 °C);

for $C_{21}H_{21}NF_2O_4$ (389.4)

calculated: 64.77 % C, 5.44 % H, 3.58 % N, 9.76 % F;

found: 64.84 % C, 5.35 % H, 3.34 % N, 9.66 % F;

^{1}H-NMR (C^2HCl_3): δ (2-CH_3) = 1.30 d, J = 7.0 Hz;

δ (NH) = 6.36 bt;

δ (aromat. ortho-CH) = 8.05 d, J = 8.5 Hz.

Similarly were prepared:

Ethylamide of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid with a 72.8 % recovery (melting point 128 °C, crystallized in ac ton);

for $C_{19}H_{19}NF_2O_2$ (331.4)

calculated: 64.77 % C, 5.44 % H, 3.58 % N, 9.76 % F;
found: 64.84 % C, 5.35 % H, 3.34 % N, 9.66 % F;
^{1}H-NMR (C^2HCl_3): δ (2-CH_3) = 1.30 d, J = 7.0 Hz;
δ (NH) = 6.36 bt;
δ (aromat. ortho-CH) = 8.05 d, J = 8.5 Hz.

Morpholide of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid with a 65.8 % recovery (melting point 95-97° C, crystallized in acetone) (n-hexane, 4:1);
for $C_{21}H_{21}NF_2O_3$ (373.4)
calculated: 67.55 % C, 5.69 % H, 3.75 % N, 10.18 % F;
found: 67.36 % C, 5.81 % H, 3.66 % N, 10.29 % F;
^{1}H-NMR (C^2HCl_3): δ (2-CH_3) = 1.22 d, J = 7.0 Hz;
δ (CH_2 morpholine) = 3.68 bs;
δ (aromat. ortho-CH) = 8.07 d, J = 8.5 Hz.

Example 2

Ethylester of 4-(2,4-difluorobiphenylyl)-4-oxobutanoic acid

1.2 ml thionylchloride is added to 20 ml ethanol, cooled to - 15° C and then, 4.0 g 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid is added in four portions while the temperature is kept at -10° C by cooling. At this temperature it is stirred for 30 minutes; then, instead of cooling the mixture is heated to 40-45° C for two hours. Ethanol is vacuum evaporated and the residue is dried by double vacuum distillation with 20 ml benzene. After crystallisation in acetone the crude product gives 3.0 g (68.5 % theor.) of ethylester (melting point 67-68° C)
for $C_{19}H_{18}F_2O_3$ (332.4)
calculated: 68.66 % C, 5.46 % H, 11.43 % F;
found: 68.41 % C, 5.41 % H, 11.37 % F;
^{1}H-NMR (C^2HCl_3): δ (2-CH_3) = 1.30 d, J = 7.0 Hz;
δ (CH_2) ester = 4.16 q, J = 7.0 Hz;
δ (arom. ortho-CH) = 8.06, J = 8.5 Hz;

Similarly were prepared:
Isobutylester of 4-(2,4-difluorobiphenylyl)-2-methyl-4oxobutanoic acid with a 90.5 % recovery (melting point 50-52° C)
for $C_{21}H_{22}F_2O_3$ (360.4)
calculated: 69.98 % C, 6.15 % H, 10.54 % F;
found: 69.78 % C, 6.16 % H, 10.28 % F;
^{1}H-NMR (C^2HCl_3): δ (CH_3 isobutyl) = 0.92 d, J = 7.0 Hz;
δ (2-CH_3) = 1.30 d, J = 7.0 Hz;
δ (aromat.ortho-CH= = 8.08 d, J = 8.5 Hz.

Example 3

n-Butylamide of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid

0.2 ml dimethylformamide is added to a suspension of 6.0 g 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid in 40 ml benzene and then, within 10 minutes 20 ml solution of thionylchloride in 20 ml benzene is added. Then, the mixture is heated to boiling (the suspension becomes a solution) and is kept at this temperature while stirring for 45 minutes. The reaction mixture is vacuum condensed and the residue redissolved in 50 ml benzene and condensed until dry. The thus obtained chloride of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid is mixed with 50 ml benzene and the solution is filtered with activated carbon. The clear filtrate is slowly added to a solution of 2.90 g of n-butylamine in 20 ml benzene cooled to 5° C. The mixture is then kept for 1 hour at 5° C and for 2 hours at 20° C. The opaque solution is washed consecutively in 100 ml 1N HCl, 100 ml H_2O, twice in 100 ml 5 % $NaHCO_3$ and again in 100 ml H_2O. After drying with magnesiumsulphate the benz n is distilled off in vacuum and th crude product is crystallized in acetone. n-butylamide of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid (melting point 114-115° C) and recovery of 72.5 % is obtained.
for $C_{21}H_{23}F_2O_3$ (359.4)
calculated: 70.18 % C, 6.45 % H, 3.90 % N, 10.57 % F;

found: 70.40 % C, 6.60 % H, 3.89 % N, 10.44 % F;
^{1}H-NMR (C^2HCl_3): δ (2-CH_3) 0 1.25 d, J = 7.0 Hz;
δ (NH) = 5.86 bt;
δ (aromat. ortho-CH) = 8.06 d, j = 8.5 Hz.

Example 4

Cyclohexylammonium salt of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid

4.0 g of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid is dissolved in 40 ml acetone and to the clear solution a solution of 1.32 g cyclohexylamine in 20 ml ether is added under constant stirring and cooling at 20 °C. Immediately a sediment begins to precipitate and ends after 2 hours of cooling at 0 °C. The precipitate is removed and thoroughly washed in cooled acetone. 4.6 g (86.1 % theoret.) of the sought product (melting point 139-140 °C) is obtained.
for $C_{23}H_{27}F_2O_3$ (403.5)
calculated: 68.47 % C, 6.75 % H, 3.47 % N, 9.42 % F;
found: 68.18 % C, 6.74 % H, 3.42 % N, 9.25 % F.

Example 5

Potassium salt of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid

A solution of 0.5 g KOH in 10 ml methanol is added to a solution og 3.05 g 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid in 30 ml acetone. The solution is evaporated to an oily residue which gives an amorphous precipitate by mixing in 40 ml ether. The precipitate is dissolved in 60 ml ethanol, the opaque solution is filtered with activated carbon and the clear filtrate is again evaporated. The oily residue is mixed with 40 ml ether and the precipitate is recovered by filtration. 2.35 g (65.3 theoret.) of potassium salt as a monohydrate (melting point 173-174 °C) is obtained.
for $C_{17}H_{13}F_2O_3K.H_2O$ (360.4)
calculated: 56.65 % C, 4.19 % H, 10.54 % F;
found: 56.71 % C, 4.04 % H, 10.39 % F.

Example 6

Calcium salt of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid

3.05 g of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid is dissolved in 55 ml 5N NaOH at 40 °C, the clear solution is heated to 70 °C and gradually, a solution of 1.1 g $CaCl_2$ is added. Upon cooling to 5 °C a precipitate is formed which after 2 hours of standing at this temperature is removed and washed on a filter with distilled water until a negative reaction for chloride ions is obtained. The precipitate is then resuspended in 50 ml distilled water, pH is adjusted to 8 with 1N HCl under constant stirring mixed for another 30 minutes and the precipitate is removed. Upon drying to a constant weight 2.7 g (83.6 % theoret.) of calcium salt of 4-(-2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid (melting point 155-157 °C) is obtained.
for $C_{34}H_{26}F_4O_6Ca$ (646.7)
calculated: 6.18 % Ca;
found: 6.42 Ca.

Example 7

L-lysine salt of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid

4.0 g of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid os dissolved in 70 ml acetone at 40 °C under constant stirring. After cooling to 20 °C a solution of 2.15 g L-lysin in 10 ml H_2O is added to th clear solution. The mixture is cooled to 5 °C and after stirring for 2 hours at this temperature the precipitate found is r moved and washed in 10 ml coiled acetone. Upon drying to a constant weight 3.5 g (59.1 % theoret.) of the product (melting point 173-175 °C) is obtained.
for $C_{23}H_{28}N_2F_2O_5$ (450.5)

calculated: 61.32 % C, 6.26 % H, 6.22 % N, 8.43 % F;
found: 61.13 % C, 6.43 % H, 6.01 % N, 8.26 % F.

Table I Pharmacological evaluation of acute toxicity[a] anti-inflammatory effect[b] in the suppression of carragenine oedema (CE) and in the inhibition of adjuvant oedema (FA) and analgesic action

Substance No.	Formula I (II) X (B^+)	mortality %	CE[c] inhibition %	FA[d] inhibition %	Pain[e] inhibition %
VUFB 18391	C_2H_5O	0	49	55	38
VUFB 18392	$C_2H_5OCOCH_2NH$	0	40	51	41
VUFB 18398	n-C_4H_9NH	0	33	44	33
VUFB 17629	(o-$C_6H_{11}NH_3^+$)	0	47	53	58
VUFB 18404	(Na^+)	30	44	51	35
VUFB 18405	(K^+)	20	39	50	47
Flobufen	OH	50	46	65	79

[a] Acute oral toxicity of each substance was evaluated after a single dose of 500 mg/kg in male mice. The mortality in % is for day 7 after application;

[b] Anti-inflammatory and analgesic activity was evaluated in comparison with flobufen in equimolar doses, while flobufen was administered in a dose of 20 mg/kg in the evaluation of anti-inflammatory activity and in a dose of 100 mg/kg in the evaluation of analgesic activity; the substances were administered orally as a suspension in a 0.5 % solution of methylcellulose and the oedema was measured 1 hour upon application;

Table I (continued)

[c] Suppression of the carraganine oedema was assessed according to Winter J.: Proc. Soc. Exptl. Biol. Med., 111, 544 (1962);

[d] Anti-inflammatory effect in the Freund-adjuvant test was assessed according to Horáková Z., Grimová J.: Cs. Fysiol. 17, 137 (1968);

[e] Analgesic activity was evaluated in the test of intraperitoneal irriation with 0.7 % acid in male mice according to Wittkin L. et al.: J. Pharmacol. 133, 400 (1961);

[f] 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid.

Table II Pharmacological evaluation of acute toxicity, anti-inflammatory and analgesic activity of substance VUFB 17640 (L-lysine salt) upon oral and parenteral application

Mode of Application	Substance	Acute Toxicity[a] Dose	% mortality	CE suppression[b] Dose	%	FA suppression[b] Dose	%	Pain suppression[b] Dose	%
Oral	17640	500	0	30	46	30	58	150	77
	Flobufen[c]	500	50	20	46	20	65	100	79
Parenteral	17640	100	0	1	21	/		80	48
				10	40				

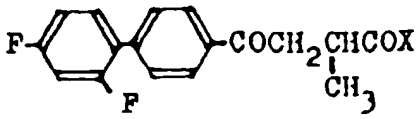
[a] Acute toxicity was evaluated after a single dose of substance 17640 in male mice, namely orally as an aqueous solution, and intravenously in physiological saline solution. Mortality was followed up in groups of 10 animals for 7 days upon oral application and for 3 days upon intravenous application;

[b] for oral and intramuscular application an aqueous solution of substance 17640 was used in said dose;

[c] the standard, i.e. 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid was administered as a suspension in a 0.5 % methylcellulose solution.

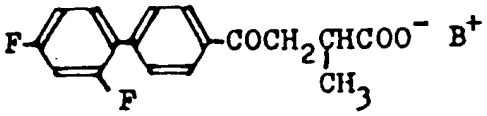
Claims

1. Functional derivatives of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid represented by following general formula (I)



(I)

wherein X stands for either OR i which R is an alkyl of 1 to 4 carbon atoms, or NHR in which R is an alkyl of 1 to 4 carbon atoms, or a $(CH_2)_nNR'_2$ group wherein n is 2 or 3 while R' is a methyl or an ethyl group; eventually X may represent morpholinyl; further salts of 4-(2,4-difluorobiphenylyl)-2-methyl-4-oxobutanoic acid with appropriate inorganic or organic bases represented by formula (II)



(II)

wherein B^+ is either an alkaline metal cation, alkaline earth cation, cyclohexylamine cation, or lysine cation.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 91109980.2

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	CHEMICAL ABSTRACTS, vol. 108, no. 5, February 1, 1988 Columbus, Ohio, USA M. KUCHAR et al. " Metabolic model and QSAR of long-acting anti-inflammatory arylaliphatic acids" page 18, abstract-no 31 304e & Pharmacochem. Libr. 1987, 10, 124-6 ----	1	C 07 C 59/88 C 07 C 69/738 C 07 C 235/34
			TECHNICAL FIELDS SEARCHED (Int. Cl.5) C 07 C 59/00 C 07 C 69/00 C 07 C 235/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	06-09-1991	HOFBAUER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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P : intermediate document

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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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